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REVIEW ARTICLE

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Differentiating pulmonary hypertension associated with protein kinase inhibitors

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Abstract

Protein kinase inhibitors (PKIs) have been implicated in pulmonary vascular toxicities including risk factors for at least three of the five World Health Organization groups of pulmonary hypertension (PH). These toxicities include direct drug-induced pulmonary arterial hypertension, an increase in cardiomyopathies, and an increase in interstitial lung disease. On- and off-target toxicities are common within multitargeted PKIs leading to cardiopulmonary toxicities. This review highlights the incidence, possible mechanisms, and management strategies for each group of possible PKI-induced PH. Future identification and clarification of protein kinase pathways for both mechanisms of toxicity and pathophysiology for PH could lead to improvements in patient care in oncology and pulmonary vascular diseases.

KEYWORDS
cancer, dasatinib, protein kinase, pulmonary arterial hypertension, tyrosine kinase

Abbreviations: ACE, angiotensin converting enzyme; ALK, anaplastic lymphoma kinase; ALL, acute lymphoblastic leukemia; ARB, angiotensin receptor blocker; ARTEMIS-IPF, Ambrisentan in Subjects with Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis; ATP, adenosine triphosphate; BCR-ABL1, breakpoint cluster region-Abelson leukemia gene; BMP, bone morphogenic protein; BNP, brain-natriuretic peptide; BTK, Bruton's tyrosine kinase; CCL2, CC ligand chemokine 2; CDK, cyclin-dependent kinase; CML, chronic myeloid leukemia; CT, computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; EGFR, epidermal growth factor receptor; ET-1 , endothelin-1; FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; FLT3, FMS-like tyrosine kinase-3; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IGF1, insulin-like growth factor 1; ILD, interstitial lung disease; IMPRES, Imatinib in Pulmonary Arterial Hypertension, a Randomized, Efficacy Study; INCREASE, Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease; IPF, idiopathic pulmonary fibrosis; LV, left ventricular; LVEF, left ventricular ejection fraction; MAPK, mitogen activated protein kinases; mPAP, mean pulmonary artery pressure; NO, nitric oxide; PAH, pulmonary arterial hypertension; PDGFR, platelet-derived growth factor; PGI_2, prostacyclin; PH, pulmonary hypertension; PI3K, phosphoinositide-3 kinase; PKI, protein kinase inhibitor; PVR, pulmonary vascular resistance; RCC, renal cell carcinoma; RHC, right heart catheterization; RISE-IIP, Riociguat for idiopathic interstitial pneumonia-associated pulmonary hypertension; ROS, reactive oxygen species; sE-selectin =, soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule; sVCAM-1, soluble vascular cell adhesion molecule; TGFB1, tumor growth factor-beta 1; VEGF, vascular endothelial growth factor; VTE, venous thromboembolism; WHO, World Health Organization.

INTRODUCTION

Pulmonary hypertension (PH) is defined by the sixth World Symposium as a mean pulmonary artery pressure of greater than 20 mmHg.[1] PH is classified into five different groups based on etiology and pathophysiology as defined by the World Health Organization (WHO). Over the last 30 years, advances in the understanding of pathophysiology, prognosis, and treatment paradigms have led to improved management of patients with PH.[2] Similarly, innovations within cancer therapeutics have led to an improvement in progression-free survival for cancer survivors. Due to improvements in mortality among cancer survivors, complications from cancer treatment are more prevalent with cardiotoxicities as one of the leading causes of death.[3]

Protein kinases inhibitors (PKIs) have become ubiquitous in the field of oncology, being used for treating leukemias, lung cancer, and melanoma, among other forms of malignancy (Table 1). Protein kinases work by transferring phosphoryl groups from adenosine triphosphate (ATP) to proteins. Phosphorylation of these kinases is crucial in cell signaling, proliferation, and survival and disruption can lead to cell death. PKIs inhibit this pathway.[95–97] Two classes of PKIs currently exist based on the binding properties and selectivity of the drug. Type I inhibitors inhibit phosphorylation via competitive binding within the ATP pocket of the substrate. Due to the ubiquity of ATP binding sites, Type I inhibitors exhibit low selectivity. Type II inhibitors demonstrate higher selectivity by binding to both the ATP pocket and an adjacent binding site.[98,99]

PKIs have been implicated in the development of PH. Different on-target and off-target toxicities of PKIs can lead to the development of PH through a variety of factors that contribute to one or multiple of the PH WHO groups.[22,23] Therefore, when a patient develops PH having been treated with a PKI, it can be challenging to determine the group of PH they fall into and the underlying etiology. specifically.[1,100–103] In this review, we discuss the various PKIs, explore their role in the development of Group 1 pulmonary arterial hypertension (PAH), Group 2 PH due to left-sided heart disease, and Group 3 PH due to lung disease and/or hypoxia. In addition, we will offer guidance as to how to clinically approach patients who develop PH in the setting of PKI treatment, based on the WHO PH classification system, and discuss management strategies.

PULMONARY ARTERIAL HYPERTENSION

WHO Group 1 PAH accounts for <3%–14%% of all cases of PH.[104,105] The pathophysiology of PAH is an imbalance in endothelial proliferation, inflammation, and remodeling within the pulmonary vasculature via three main pathways: nitric oxide (NO), endothelin-1 (ET-1), and prostacyclin (PGI_2) pathways.[106] Prolonged disproportionality of these pathways leads to dysregulation of inflammation, apoptosis, and proliferation of the smooth muscle and endothelial cells of the pulmonary artery causing an increase in mean pulmonary artery pressure (mPAP).[107] While the complexity of PAH pathophysiology extends beyond the NO, ET-1, and PGI_2 pathways, PKIs can contribute to disparities in these pathways potentially leading to direct drug-induced PAH (Table 1).

PKIs that have been implicated in Group 1 PAH are dasatinib, bosutinib, ponatinib, and nilotinib. These agents, along with imatinib, are breakpoint cluster region-Abelson leukemia gene (BCR-ABL1) inhibitors. They have been groundbreaking for the treatment of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) and have varying cardiovascular profiles. Imatinib, the first Food and Drug Administration (FDA) approved BCR-ABL1 inhibitor, has been associated with improvements in hemodynamics of pulmonary pressures and was studied for the treatment of PAH in the IMPRES trial (Imatinib in Pulmonary Arterial Hypertension, a Randomized, Efficacy Study) demonstrating an improvement in functional capacity and hemodynamics.[108–110] Although serious adverse events and study drug discontinuations were seen with imatinib in PAH, limiting its clinical use, the proposed mechanisms through which imatinib effects the pulmonary vasculature include, inhibition of platelet-derived growth factor-α/β (PDGFR-α/β), decrease proliferation of pulmonary artery smooth muscle cells, and a decrease in calcium influx resulting in pulmonary artery vasodilation.[4,111,112]

In contrast to imatinib, dasatinib, a second-generation BCR-ABL1 inhibitor has been associated with rare, but fatal PAH.[22,24] Inflammation of the pulmonary artery smooth muscle cells and elevations of T lymphocytes, leukocytes, monocytes, and macrophages is thought to be the primary mechanism of dasatinib toxicity. Rat studies have demonstrated that dasatinib predisposes those with chronic hypoxia or monocrotaline with an exaggerated worsening of pulmonary pressures.[23] Additionally, increased endothelial dysfunction as indicated by elevated levels of reactive oxygen species (ROS), soluble intercellular adhesion molecule (sICAM)-1, soluble vascular cell adhesion molecule (sVCAM)-1, and soluble E-selectin (sE-selectin) may be contributing.[112,113] Furthermore, potential off-target inhibition of Src, a non-receptor tyrosine kinase family, can lead to pulmonary vascular remodeling.[114] The Src kinase family is instrumental in phosphorylating and activating TWIK-related acid-sensitive potassium channel-1 (TASK-1) on

TABLE 1 FDA-approved PKIs with on- and off-target receptors, uses, and adverse drug effects according to WHO Group (as of February 2022)

Drug	Receptors[4,5]	Year approved	Uses	Group 1 risk factors	Group 2 risk factors	Group 3 risk factors
ALK inhibitors						
Alectinib[a6]	ALK	2015	NSCLC			ILD
Brigatinib[a7,8]	ALK, ErbB1	2017	NSCLC	PAH	HTN	ILD
Ceritinib[a9,10]	ALK	2014	NSCLC	PAH		ILD
Crizotinib[a11,12]	ALK, MET	2011	NSCLC	PAH		ILD
Lorlatinib[9,13]	ALK, ROS1	2018	NSCLC	PAH		ILD
BTK inhibitors						
Acalabrutinib[a14]	BTK	2017	CLL, SLL, MCL		HTN, AF	
Ibrutinib[a15]	BTK	2013	CLL, GVHD, MCL, MZL, SLL, WMG		HTN, AF, HFrEF	
Zanubutinib[16]	BTK	2019	MCL		HTN, AF	
BCR-ABL1 inhibitors						
Asciminib[17]	BCR-ABL1, STAMP	2021	CML		HTN, HFrEF	
Bosutinib[a18–21]	BCR-ABL1, Src, FGFR1-3, VEGFR1-2, FLT3, PDGFRα/β	2012	CML	PAH	HTN, HFrEF	
Dasatinib[a22–26]	BCR-ABL1, FGFR, KIT, PDGFRα/β, Src	2006	ALL, CML, GIST	PAH	HTN, HFrEF	
Imatinib[27]	BCR-ABL1, FLT3, KIT, PDGFRα/β	2001	ALL, ASM, CEL, CML, DFSP, HES, GIST, MDS/MPD		HTN, HFrEF	
Nilotinib[28–30]	BCR-ABL1, FLT3, KIT, PDGFRα/β	2007	ALL, CML, GIST	PAH	AF	
Ponatinib[29,31–33]	BCR-ABL1, FGFR, VEGFR1-3, FLT3, KIT, PDGFRα/β, Src, TIE2	2012	ALL, CML	PAH	HTN, HFrEF	
BRAF/MEK inhibitors						
Binimetinib[a34]	MEK1/2	2018	Melanoma, CRC		HFrEF, HTN	ILD
Cobimetinib[35]	MEK1	2015	Melanoma		HFrEF, HTN	
Dabrafenib[a36]	BRAF	2013	Melanoma, NSCLC, TC		HFrEF	
Encorafenib[a37]	BRAF	2018	CRC, Melanoma			
Selumetinib[38]	MEK1/2	2020	NF1		HFrEF, HTN	
Trametinib[39]	MEK1/2	2013	Melanoma, NSCLC, TC		HTN, HFrEF	ILD
Vemurafenib[a40]	BRAF	2011	Melanoma, ECD, NSCLC		AF, HTN	
CDK-4/6 inhibitors						
Abemaciclib[a41]	CDK-4/6	2017	BC			ILD
Palbociclib[a42]	CDK-4/6	2015	BC			ILD

(Continues)

TABLE 1 (Continued)

Drug	Receptors[4,5]	Year approved	Uses	Group 1 risk factors	Group 2 risk factors	Group 3 risk factors
Ribociclib[a43]	CDK-4/6	2017	BC			ILD
Trilaciclib[44]	CDK-4/6	2021	Chemo-induced myelosuppression			ILD
ErbB inhibitors						
Afatinib[a45]	ErbB1, ErbB2, ErbB4	2013	NSCLC		HFrEF	ILD
Dacomitinib[46]	ErbB1, ErbB2, ErbB4	2018	NSCLC			ILD
Erlotinib[a47]	ErbB1	2004	NSCLC, PC			ILD
Gefitinib[a48,49]	ErbB1	2015	NSCLC			ILD
Lapatinib[a50]	ErbB1, ErbB2, ErbB4	2007	BC		HFrEF	ILD
Mobocertinib[51]	ErbB1, ErbB2, ErbB4	2021	NSCLC		AF, HTN, HFrEF	ILD
Neratinib[a52]	ErbB1, ErbB2	2017	BC			
Osimertinib[a53]	ErbB1	2015	NSCLC		HFrEF	ILD
Tucatinib[54]	ErbB2	2020	BC			
FGFR inhibitors						
Erdafitinib[55]	FGFR	2019	UC		HFrEF	
Infigratinib[56]	FGFR	2021	Cholangio-carcinoma			
Nintedanib[a57]	FGFR, VEGFR1-3, Src, PDGFR, CSF1	2014	ILD/IPF		HTN	
Pemigatinib[58]	FGFR	2020	Cholangio-carcinoma			
FLT3 inhibitors						
Gilteritinib[59]	FLT3, AXL, ALK	2018	AML		HFrEF	ILD
Midostaurin[a60]	FLT3, VEGFR2, KIT, PDGFR	2017	AML, MCL, ASM		HTN, HFrEF	ILD
JAK inhibitors						
Abrocitinib[61]	JAK 1	2022	Atopic dermatitis		HTN	
Baricitinib[a62]	JAK1/2	2018	RA			
Fedratinib[63]	JAK2, FLT3	2019	Myelofibrosis		HTN, HFrEF	
Ruxolitinib[a29,64,65]	JAK1/2	2011	Atopic dermatitis, GVHD, Myelofibrosis, PV	PAH	HTN	
Tofacitinib[a66]	JAK1-3	2012	RA, PsA, Ulcerative colitis		HTN	ILD
MET inhibitors						
Capmatinib[67]	MET	2020	NSCLC			ILD
Tepotinib[68]	MET	2021	NSCLC, thyroid cancer			
mTOR inhibitors						
Everolimus[69]	mTOR	2009	BC, NT, RCC, TS, transplants, WMG		HTN	ILD
Sirolimus[70]	mTOR	1999	GVHD, LAM, transplants		HTN	ILD

TABLE 1 (Continued)

Drug	Receptors[4,5]	Year approved	Uses	Group 1 risk factors	Group 2 risk factors	Group 3 risk factors
Temsirolimus[71]	mTOR	2007	Endometrial cancer, RCC		HTN	ILD
PDGFR inhibitors						
Avapritinib[72]	PDGFRα, KIT	2020	GIST		HTN	
Ripretinib[73]	PDGFRα, KIT	2020	GIST		HTN, HFrEF	
PI3K-δ inhibitors						
Copanlisib[a74]	PI3K-δ	2017	FL		HTN	ILD
Idelalisib[a75]	PI3K-δ	2014	CLL, FL, SLL			ILD
Umbralisib[76]	PI3K-δ	2021	FL, MZL			ILD
RET inhibitors						
Pralsetinib[77]	RET, DDR1, JAK1/2, TRKA/C, PDGFRβ, FGFR	2020	NSCLC, TC		HTN	ILD
Selpercatinib[78]	RET, VEGFR1/3, FGFR	2020	NSCLC, TC		HTN	
Vandetanib[a79]	RET, ErbB1, VEGFR2, TIE2, Src	2011	TC		HTN, HFrEF	ILD
TRK inhibitors						
Entrectinib[80]	TRKA/B/C, ROS1, ALK	2019	NSCLC, NTRK + solid tumors		HTN, HFrEF	
Larotrectinib[81]	TRKA/B/C	2018	NTRK + solid tumors		HTN	
VEGF inhibitors						
Axitinib[a82]	VEGF1-3, FGFR	2012	RCC, TC		HTN, HFrEF	
Cabozantinib[83]	VEGFR1-3, MET, RET, KIT, FLT3, TIE2, TRKB, AXL	2012	HCC, RCC, TC		HTN	
Lenvatinib[a84]	VEGFR1-3, FGFR, PDGFRα, KIT, RET	2015	Endometrial cancer, HCC, RCC, TC		HTN, HFrEF	
Pazopanib[a85]	VEGFR1-3, KIT, PDGFRβ	2009	RCC, Soft tissue sarcoma, TC		HTN, HFrEF	ILD
Regorafenib[86]	VEGFR2/3, RET, KIT, PDFGR, BRAF	2012	CRC, GIST, HCC, osteosarcoma		HTN	
Sorafenib[87]	VEGFR1-3, FLT3, PDGFRα/β, BCR-ABL1, FGFR	2005	Angiosarcoma, GIST, HCC, RCC, TC		HTN, HFrEF	ILD
Sunitinib[a88]	VEGFR1-3, FLT3, PDGFRα/β, BCR-ABL1, FGFR, Src	2006	GIST, PC, RCC		HTN, HFrEF	
Tivozanib[89]	VEGF	2021	RCC		HTN, HFrEF	
Other						
Belumosudil[90]	ROCK1, ROCK2	2021	GVHD		HTN	
Fostamatinib[a91]	Syk	2018	ITP		HTN	

(Continues)

TABLE 1 (Continued)

Drug	Receptors[4,5]	Year approved	Uses	Group 1 risk factors	Group 2 risk factors	Group 3 risk factors
Netarsudil[92]	Rho	2017	Glaucoma			
Pexidartinib[93]	CSF1, KIT, FLT3	2019	Tenosynovial giant cell tumor		HTN	

Abbreviations: ALK, anaplastic lymphoma kinase; ALL, acute lymphoblastic leukemia; ASM, aggressive systemic mastocytosis; AXL, AXL oncogene; BC, breast cancer; BCR-ABL1, breakpoint cluster region-Abelson leukemia gene; BTK, Bruton's tyrosine kinase; BRAF, b-Raf oncogene; CEL, chronic eosinophilic leukemia; CDK, cyclin-dependent kinase; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CRC, colorectal cancer; CSF1, colony-stimulating factor 1; DFSP, dermatofibrosarcoma protuberans; ECD, Erdheim-Chester disease; ErbB1/EGFR, epidermal growth factor receptor; ErbB2/HER2, human epidermal growth factor receptor 2; ErbB4/HER4, human epidermal growth factor receptor 4; FGFR, fibroblast growth factor receptor; FL, follicular lymphoma; FLT3, Fms-like tyrosine kinase 3; GIST, gastrointestinal stromal tumor; GVHD, graft versus host disease; HTN, hypertension, HFrEF, heart failure with reduced rejection fraction, HES, hypereosinophilic syndrome; HA, hemolytic anemia; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; ITP, immune thrombocytopenia; JAK, Janus kinase; KIT, c-KIT oncogene; LAM, lymphangioleiomyomatosis; MCL, mantle cell lymphoma; MEK1/MAPK, mitogen-activated protein kinase kinase 1; MET/HGHR, hepatocyte growth factor receptor; MDS/MPD, myelodysplastic/myeloproliferative disorder; mTOR, mechanistic target of rapamycin; MZL, marginal zone lymphoma; NF1, neurofibromatosis type 1; NSCLC, non-small cell lung cancer; NT, neuroendocarine tumor; NTRK, neurotrophic receptor kinase; PAH, pulmonary arterial hypertension; PC, pancreatic cancer; PDGFR, platelet-derived growth factor receptor; PI3K-δ, phosphoinositide-3 kinase delta; PsA, Psoriatic arthritis; PV, polycythemia vera; RA, rheumatoid arthritis; RET, rearranged during transfection oncogene; Rho, Rhodopsin oncogene; ROCK, rho-associated, coiled-coil containing protein kinase; ROS1, C-ros oncogene 1; SLL, small lymphocytic lymphoma; Src, Src oncogene; STAMP, specifically targeting the ABL myristoyl pocket; Syk, Spleen-associated tyrosine kinase; TC, thyroid cancer; TE, thromboembolic event; TIE2, tyrosine kinase with Ig and EGF homology domains 2; TRK, tropomyosin receptor kinase; TS, tuberous sclerosis; UC, urothelial carcinoma; VEGFR, vascular endothelial growth factor receptor; WMG, Waldenström macroglobulinemia.

[a]Denotes known Type I inhibitor.[94]

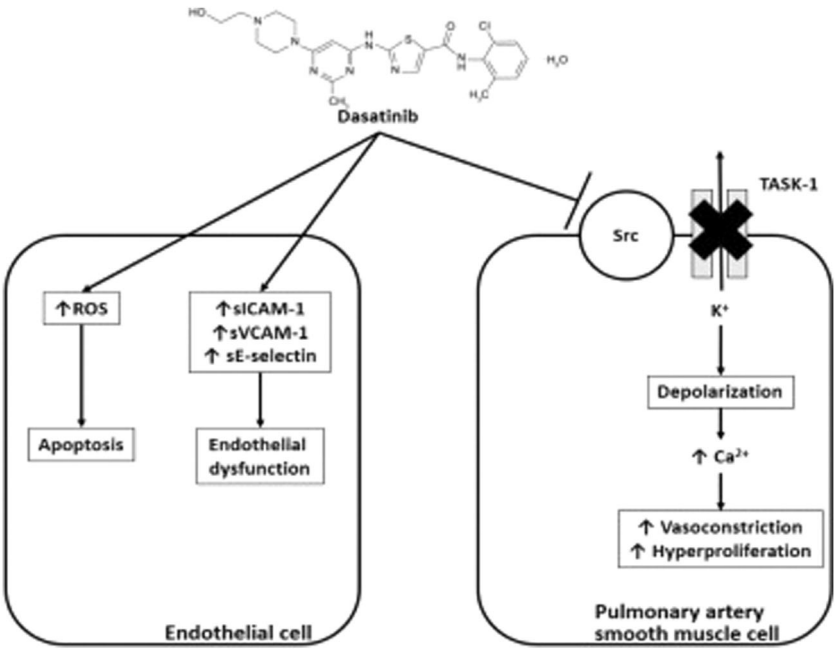

FIGURE 1 Mechanism of dasatinib-induced PAH. PAH, pulmonary arterial hypertension; ROS, reactive oxygen species; sE-selectin, soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule; sVCAM-1, soluble vascular cell adhesion molecule

the pulmonary artery smooth muscle cells leading to vasodilation.[114] Inhibition of the TASK-1 channels causes a depolarization of the smooth muscle cell leading to an increase in intracellular calcium via L-type voltage-gated calcium channels. This Src kinase inhibition could explain why imatinib might have a therapeutic effect in PAH, whereas dasatinib has been shown to cause PAH.[112] (Figure 1) The PKI pathway continues to be explored therapeutically in PAH. One such example is with a novel inhaled PDGFR kinase inhibitor, seralutinib (Gb002), which in animal studies improved hemodynamics, NT-proBNP, and pulmonary vascular remodeling.[115] Imatinib is also being explored in aerolized forms. In theory, both of these agents will be expected to have less adverse events due to the localized delivery system and are currently being studied in

clinical trials.[116,117] In addition, oral imatinib remains under consideration as a potential PAH therapy.

Bosutinib, ponatinib, and nilotinib have less evidence with only rare case reports or limited of worsening pre-existing PAH, some of which only found echocardiographic evidence of PH.[18–20,28,31,118,119] A recent pharmacovigilance study supports the Src family kinase postulation indicating that the c-Src, c-yes, Lck, and Lyn genes (members of the Src kinase family) are implicated in a disproportionately high incidence of PAH within the BCR-ABL1 inhibitors that are dose-related.[29]

Anaplastic lymphoma kinase (ALK)-inhibitors, brigatinib, ceritinib, crizotinib, lorlatinib are used in the treatment of non-small cell lung cancer and have also been implicated in the development of PAH, with lorlatinib being the most implicated.[7,9,11] The causative mechanism of action of these agents in the development of pulmonary vascular disease is unknown although typical histologic findings of PAH are seen, namely intimal hyperplasia, medial hypertrophy, and angioproliferative plexiform lesions, plus sporadic peripheral arterial thrombosis in situ.[7]

The difficulty of predicting the long-term effects of PKIs on pulmonary vascular toxicity may result in a failure to prevent adverse effects and may delay the use of life-saving PAH therapies. For example, several guidelines recommend regular monitoring for the development of cardiotoxicity with some chemotherapy drugs, but specific recommendations are not provided for pulmonary vascular toxicity.[120,121] Within our program, the practice is to perform echocardiograms every 3 months on patients receiving PKIs. If patients have evidence of PH on echocardiogram, accompanied by rapid symptom onset or progression, they would be referred for urgent right heart catheterization (RHC) to evaluate for the presence of PAH. If PH is uncovered on echocardiogram and the patients are minimally symptomatic and display marginally progressive echocardiogram features, then these patients can be followed with serial echocardiograms to observe the development of early right ventricular failure or signs of early clinical decompensation. Patients are referred for RHC only if there is significant progression of disease or if there are questions regarding optimum oncological therapy. If patients have significant risk factors for Group 2 PH, then they are followed serially rather than referred for invasive hemodynamics, unless there is concern for the concomitant development of Group 1 PAH.[122]

Early discontinuation of the culprit agent can lead to a reversal of the pulmonary vascular disease.[18–20,22,25,28,118] Rapid clinical and hemodynamic improvements were noted within 4 months of discontinuation of dasatinib, although a more recent study found that PAH persisted in approximately one-third of patients.[22,25]

The management of PKI-induced PAH varies depending on the long-term complications of the therapy. Pharmacotherapy for persistent PAH revolves around standard PAH-therapy protocols.[101] In the absence of high-risk features, or the development of right heart failure, our practice is to start upfront dual combination therapy.[102,123] This involves an endothelin receptor antagonist (ERA) combined with a phosphodiesterase 5 inhibitor (PDE5i). Within our program, we combine ambrisentan or macitentan with either sildenafil or tadalafil, once PAH is confirmed on RHC. If there is a concern regarding acute right heart failure, this requires initiation of parenteral prostacyclins. However, with the exception of dasatinib, most cases of PKI-induced PAH are low- to intermediate-risk, and cessation of the PKI combined with long-term use of dual combination therapy is sufficient to prevent or postpone clinical demise.

PH DUE TO LEFT HEART DISEASE

Group 2 PH is the most prevalent form of PH accounting for upwards of 68.5% of PH patients, encompassing heart failure with reduced ejection fraction (HFrEF), heart failure with preserved (HFpEF), and valvular heart disease.[105,124] The association between PKI therapy and heart failure appears to be indirect and mediated by increase in left ventricular end-diastolic pressure from elevated blood pressure.[125] Alternatively, a direct effect may be the antiangiogenesis in capillarization of the myocardium itself, which impairs the preservation of functional status.[126] Of note, while bilateral pleural effusions may be associated with heart failure, certain PKIs, for example, dasatinib, have been shown to increase the permeability of endothelial cells leading to effusions independent of a heart failure diagnosis.[127] Hypertension remains the commonest modifiable risk factor for the development of heart failure and almost every group of PKIs is associated with the development of hypertension and heart failure (Table 1).[128] The pathophysiology contrasts with Group 1 and these cases can be distinguished by an increased left ventricular end-diastolic pressure. In this setting, if there is concern for PH secondary to PKI therapies, an RHC is warranted to determine the optimum treatment strategy and a need to distinguish between Group 1 and Group 2 PH,[124] although, combined pre- and post-capillary PH secondary to dasatinib has been reported.[25]

Hypertension and atrial fibrillation are co-morbidities linked to the development of HFpEF.[129] Select PKIs,

specifically VEGF inhibitors, such as sorafenib and sunitinib, and Bruton's tyrosine kinase inhibitors (BTKs), such as ibrutinib and acalabrutinib, are known to increase hypertension and atrial fibrillation. VEGF inhibitor-induced hypertension is a multifactorial mechanism. First, vasodilation occurs from VEGFR2 activation of phosphoinositide-3 kinase (PI3K) increasing downstream endothelial NO synthase phosphorylation and thus NO release.[130] VEGFR2 activation also leads to increases PGI_2 via activation of mitogen-activated protein kinases (MAPKs).[131] Antagonism of these pathways in addition to glomerular damage from increased ET-1 production lead to the on-target toxicity from VEGF inhibitors.[130] Decreases in microvascular and myocardial capillary density could lead to increases in vascular resistance and endothelial dysfunction.[131] Additionally, some PKIs, such as ponatinib, have off-target VEGF inhibition not related to their therapeutic target. The most effective blood pressuring lowering agent is unknown, but both calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors appear effective.[132]

The BTK inhibitors, acalabrutinib, ibrutinib, and zanubutinib. may increase the risk of HFpEF by elevating blood pressure, inducing atrial fibrillation, and other off-target effects involving C-terminal Src kinase inhibition causing left atrial inflammation, fibrosis, and enlargement.[133] Ibrutinib can cause hypertension within a few months of treatment and is associated with upwards of 75% of patients developing or worsening hypertension.[134] Atrial fibrillation has a 16% occurrence rate with ibrutinib.[135] Of note, more selective BTK inhibitors, acalabrutinib and zanubrutinib, do not carry the same risk of hypertension or atrial fibrillation to the extent of ibrutinib.

More recently, PKIs have been related to the development of valvular dysfunction. One culprit is the BCR-ABL1 inhibitor, nilotinib which has been associated with rapid progression of aortic valve stenosis. The mechanism behind this is theorized to be related to an increase in BMP2 related valvular interstitial cell calcification.[136]

VEGF inhibiting PKIs have also been associated with the development of HFrEF. While the incidence is difficult to estimate, two meta-analyses described a higher risk of developing cardiomyopathy among people treated with VEGF inhibitors (odds ratio: 1.35 (95% confidence interval [CI]: 1.06–1.70) and 2.53 (95% CI: 1.79–3.57)).[137,138] Sunitinib treats renal cell carcinoma and targets the VEGF receptors to produce antiproliferative and antiangiogenesis effects (RR: 2.96; 95% CI: 1.93–4.53) and has the highest risk of causing cardiomyopathy (prevalence of ~10%).[137,138] Due to its wide selectivity, sunitinib also inhibits PDGFR-α/β, FMS-like tyrosine kinase-3 (FLT3), fibroblast growth factor receptors (FGFR), and multiple other receptors. While the exact mechanism of left ventricle (LV) dysfunction from sunitinib is unknown and is likely multifactorial; it could be a sequela of hypertension associated with VEGF inhibition (on-target) or due to inhibition of FGFR, which are important to LV functionality (off-target).[139–141] Fortunately, in patients who develop LV dysfunction from sunitinib, withdrawal of the medication appears to lead to improvement in LV dysfunction and heart failure symptoms.[141]

Management of PKI-induced Group 2 PH includes screening left ventricular ejection fraction (LVEF) and blood pressure along with management of any baseline cardiovascular risk factors.[142] For hypertension, ACE inhibitors and angiotensin receptor blockers (ARBs) are the preferred agents, as calcium channel blockers (specifically verapamil and diltiazem) can cause *CYP3A4* interactions. A recent publication compiled the recommendations from European and American guidelines for the management of cardiotoxicities in cancer patients.[142] Laboratory screening of biomarkers such as brain-natriuretic peptide (BNP)/NT-proBNP and troponin can also be considered. After initial evaluation, follow-up screening can be considered every 3 months during treatment or sooner if symptoms develop. In patients who experience a decrease in LVEF, a referral for a cardio-oncological evaluation and the initiation of ACE inhibitors and β-blockers are recommended (Figure 2), in addition to other guideline-directed medical therapy for cardiomyopathy as needed. If the patient is symptomatic and/or the LVEF is <40%, discontinuation of the therapy is recommended. If the patient is asymptomatic with an LVEF ≥ 40%, continuation of therapy can be considered with close monitoring. Consultation from an expert cardio-oncology center is recommended to navigate the complex treatment environment associated with Group 2 PH and cancer.[143]

PH DUE TO CHRONIC LUNG DISEASE AND HYPOXIA

PH due to chronic lung disease and hypoxia is the second most common form of PH.[105,144] PKIs are implicated in interstitial lung disease (ILD) and idiopathic pulmonary fibrosis (IPF), purely in the parenchymal space.[145] ILD was first noted as a complication of gefitinib, an epidermal growth factor receptor (EGFR) inhibitor in

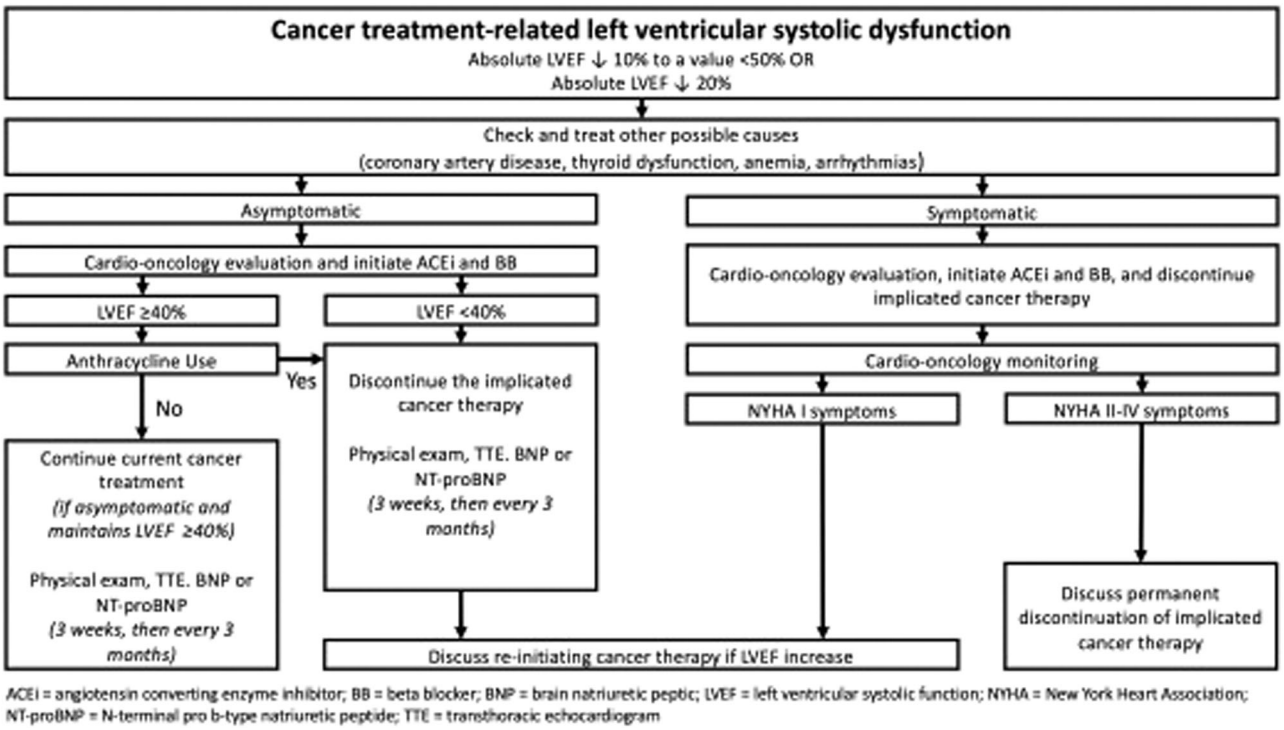

FIGURE 2 Definitions and management of overt cancer therapy-related left ventricular systolic dysfunction (adapted from ref. [142]). ACEi, angiotensin-converting enzyme inhibitor; BB, beta-blocker; BNP, brain natriuretic peptic; LVEF, left ventricular systolic function; NYHA, New York Heart Association; NT-proBNP, N-terminal pro b-type natriuretic peptide; TTE, transthoracic echocardiogram

the early 2000s.[146] ILD developed typically within days of initiation, but could occur up to 3 months after starting therapy. The prevalence of ILD with gefitinib was <1%, but with a high mortality of up to 35%.[48,145] In IPF, a PH has been reported in 8%–15% of patients upon initial diagnosis with increasing prevalence up to >60% in advanced and end-stage disease.[147–149] Additionally, a high prevalence of PH in ILD was noted in an echocardiographic study.[150] In this manner, it is reasonable to assume that PKI-induced ILD could be associated with PH, no least through hypoxic pulmonary vasoconstriction alone.

Cyclin-dependent kinase (CDK)-4/6 inhibitors, ErbB inhibitors, and FLT3 inhibitors are the commonest causes of PKI-induced ILD (Table 1), but can also occur with the use of ALK inhibitors, such as brigatinib.[151] Contrary to most forms of ILD, PKI-induced ILD has nonspecific changes with the parenchymal tissue on high-resolution computed tomography (CT) that is difficult to diagnose.[152] Nonspecific areas with ground-glass opacities without loss of lung volume are the most common pattern accounting for 50% of PKI-induced ILD. The toxicity does not appear to be dose related, and the mechanism remains largely unknown.[153] Recent bioinformatics studies indicate that the four genes with the highest association with ILD development include EGFR, tumor growth factor β-1 (TFGB1), insulin-like growth factor 1 (IGF1), and CC ligand chemokine 2 (CCL2).[154] Further investigation into the exact mechanism of these pathways may elucidate the on- and off-target toxicities of PKIs that lead to ILD.

For patients on PKIs that develop pulmonary symptoms or suspected ILD, the PKI should be held.[145] Furthermore, switching to another PKI appears to be safe with no recurrence of ILD, indicating a lack of cross-reactivity between agents.[145] Also, as symptoms improve, one can consider rechallenging the person with the PKI after discussing the risk versus benefit of treatment.[155] The use of high-dose corticosteroids has been used in other forms of drug-induced ILD (i.e., taxanes and gemcitabine) and may be useful in PKI-induced ILD.[146] Otherwise, there is conflicting evidence in using PAH-specific therapies Group 3 PH in this population.[144] Riociguat and ambrisentan have been shown to be harmful in patients with idiopathic interstitial pneumonia as noted in the RISE-IIP and ARTEMIS-IPF studies.[156,157] There is evidence that inhaled treprostinil (INCREASE trial) improves symptoms in ILD-associated PH.[158] Although not specifically studied in PKI-induced ILD, inhaled treprostinil could be considered in this group, especially if withdrawal of the offending agent does not result in clinical improvement.

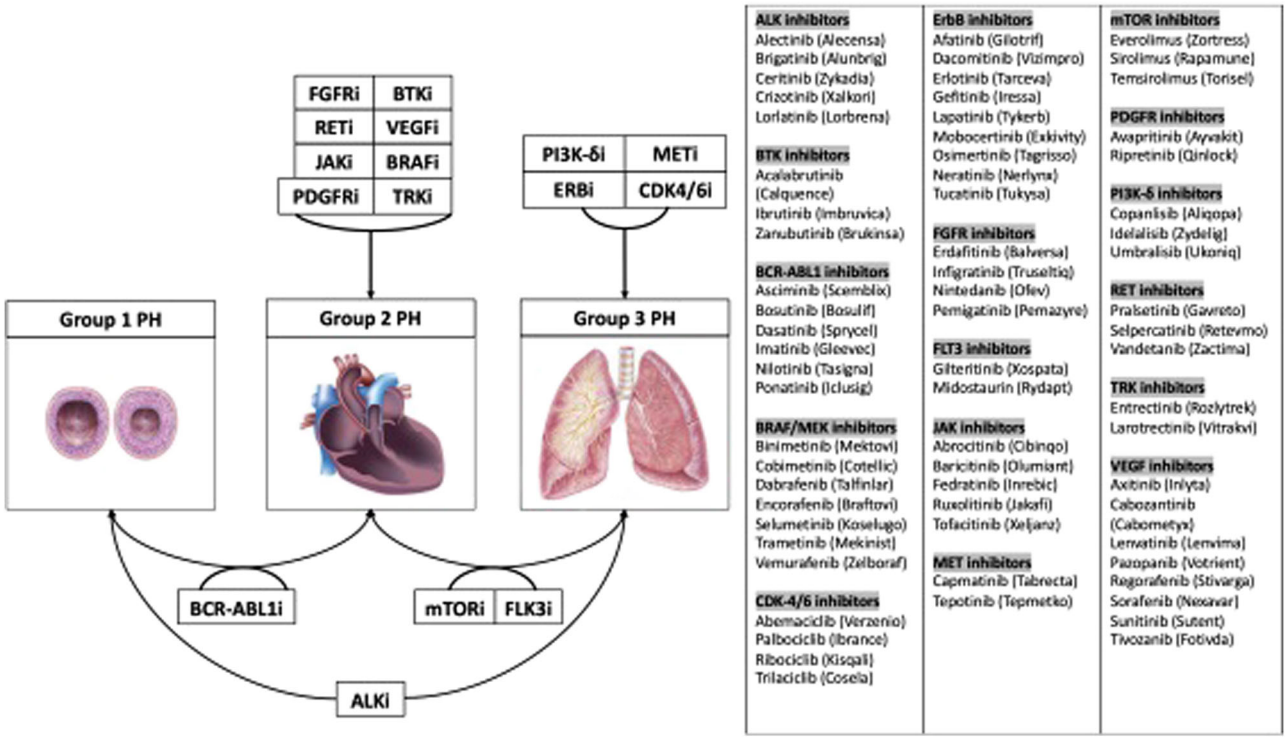

FIGURE 3 Connecting PKI groups with the likely WHO PH class. ALK, anaplastic lymphoma kinase; BCR-ABL1, breakpoint cluster region-Abelson leukemia gene; BRAF, b-Raf oncogene; BTK, Bruton's tyrosine kinase; CDK, cyclin-dependent kinase; ErbB1/EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; FLT3, Fms-like tyrosine kinase 3; JAK, Janus kinase; MEK, mitogen-activated protein kinase; MET/HGHR, hepatocyte growth factor receptor; mTOR, mechanistic target of rapamycin; PDGFR, platelet-derived growth factor receptor; PI3K-δ, phosphoinositide-3 kinase delta; RET, rearranged during transfection; TRK, tropomyosin receptor kinase; VEGFR, vascular endothelial growth factor receptor

CONCLUSION

Targeted PKI therapies for malignancies have revolutionized treatment for many patients with cancer. However, increasing cardiotoxicities are being identified as both on- and off-target effects, including effects on the pulmonary vasculature. Cardiac screening and cardio-oncology programs have typically focused on the effects of cancer therapeutics on the left ventricle and systemic vasculature.[143,159] Growing awareness of PH and the risks associated with PKIs and other novel targeted therapies is important in this population, as is understanding which agents are implicated in the different forms of PH (Figure 3). This review provides a roadmap for the management of PH in the setting of PKI therapy and highlights the ongoing challenges that these patients face.

FUTURE DIRECTIONS

The ongoing identification of PKI toxicities plays a crucial role in determining treatment options for patients who develop PH while undergoing cancer treatment. Advancements in bioinformatics and genomics research, in conjunction with large electronic databases, improve detection of PKI toxicities,[29,160] as it pertains to the pulmonary vasculature. Such advances may also help identify PKIs with therapeutic potential.[112]

AUTHOR CONTRIBUTIONS

Joshua A. Jacobs contributed by designing the concept, writing, correcting the manuscript, and creating tables. John J. Ryan contributed by designing the concept, writing, correcting the manuscript, and creating figures. Eiman Jahangir contributed by writing and correcting the manuscript. All authors have reviewed and acknowledged the accuracy of this review paper.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICS STATEMENT

The ethics statement is not available.

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